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Kako tolmačiti histološke izvide sluznice pri diagnosticiranju gastro-intestinalnih bolezni pri otrocih

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Abstract

The gastrointestinal system includes multiple organs through which food passes, nutrients are absorbed and waste is eliminated. It also has endocrinologic and immunologic functions. Many diseases can affect the digestive system. In differential diagnosis workup, laboratory tests, imaging but most of all endoscopic and histologic examination are helpful.

For proper specimen interpretation, an effective dialogue between the pathologist and the clinician, is necessary.

Izvleček

Prebavni sistem vključuje več organov, skozi katere prehaja hrana, se vsrkavajo hranila in izločajo odpadki. Ima tudi endokrinološko in imunološko funkcijo. Na prebavni sistem lahko vpliva veliko bolezni. Za diferencialno diagnozo so koristni rezultati laboratorijskih preiskav in slikovnih preiskav, a večinoma predvsem endoskopski in histološki pregled.

Za pravilno tolmačenje histoloških vzorcev je pomemben dober dialog med endoskopistom in patologom.

Introduction

Gastrointestinal (GI) tract is a complex and dynamic organ that includes many specialized parts and functions. It serves as the digestive organ of the body that is involved in absorption and metabolism of nutritiens and excretion of nondigestible and toxic products. By neuromuscular interactions, food and liquids move through different sections of the gastrointestinal tract for digestion and absorption. Throughout lifetime, it is continuously exposed to different antigens, toxins and infectious organisms, which provoke immunological system, but also result in some diseases. Generally, this occurs when the integrity of the gastrointestinal tube wall is compromised. Functions of immunological and endocrine systems also influence disease development, as well as high migration and fast proliferation rate in almost all parts of the digestive system.[1]

From the basal layers of mucosa, crypts or glands, cells migrate to superficial parts to lumen or undergo apoptosis. Whole process in different parts takes 4 to 6 days. Some nutritional and toxic stimuli, surgical interventions as well as physiological and pathological states influence renewal and adopting. Unipotential and pluripotential stem cells in the gastrointestinal wall, but also in adjacent organs and lymph nodules, have a major role in this process.

The gastrointestinal tube is composed of four concentric layers: mucosa, submucosa, muscularis propria and serosa.

The mucosa consists of epithelium, lamina propria with immunocompetent cells and muscularis mucosa. Epithelia are different in each major part of the GI tube and somewhere form glands, ducts, crypts and vili, which mean a different function as well. The lamina propria is a connective tissue with lymphocytes, macrophages, mast cells, eosinophils, neutrophils and plasma cells which secret different immunoglobulins. It also contains gut-associated lymphoid tissue (GALT) and other parts of immunologic

system, but also vessels and unmyelinated nerve fibres.

Mast cells have role in acute inflammation and chronic inflammatory changes, so they participate in most gastrointestinal diseases, including food allergies, eosinophilia, immunodeficiencies and immediate hypersensivity reactions, host responses to parasites and neoplasms, inflammatory and fibrotic diseases.

Eosinophils in lamina propria have function in host defence, including the phagocytosis and killing microbes, but also in allergic reactions.

The submucosa is less cellular than the mucosa. It contains fat, major blood vessels, nerves, lymphatics, ganglia and lymphoid collections.

The muscularis propria have two smooth muscle layers. They also form sphincters and as a major pacemaker serve intestinal cells of Cajal. In case of any abnormality, motility disorders and GI stromal tumors occurred.

Serosa/adventitia is made of connective tissue with fat, collagen and elastic fibres.[2,3]

Gastrointestinal specimens

Biopsies are important in establishing a specific diagnosis or in following the evolution of a lesion or disease, its extent, severity or malignant transformation. We also take biopsies for microbial culture, biochemical examination, ultrastructural examination or for molecular markers.

It is important that endoscopist indicate the exact site of the origin of biopsy, separate multiple location specimens in different tubes and properly describe endoscopic location and corresponding findings. It will be ideal if every specimen is oriented, for example on paper, to avoid tangential cutting.

Specimens should be placed in an adequate amount of fixative (10 % buffered formalin, glutaraldehyde or else), at least five times the volume of the specimens. Some tissue needs to be fresh frozen for some immunologic and genetic or chromosomal studies.[3]

There are some critical points in the histology of paediatric gastrointestinal diseases that are important for differential diagnosis and treatment.

Esophagus

Typical oesophageal epithelium is squamous, except in the distal end where there is the squamocolumnar junction. This junction is very important part of the oesophagus because the most important changes can be found there. The main clinical, endoscopic and histological differentiation between oesophageal and gastric mucosa is resistance to acid. The dominant pathophysiological mechanisms that cause gastro-oesophageal junction incompetence are transient lower oesophageal sphincter relaxations, inconsistency of lower oesophageal sphincter and anatomic disruption of the gastro-oesophageal junction.[4]

Chronic disease that develops when the reflux of stomach acid causes symptoms and/or complications is gastro-oesophageal reflux disease (GORD). Symptoms of GORD are retrosternal and epigastric burning sensations, difficulty in swallowing, pain, vomiting and nausea, sore throat, hoarseness, cough, etc. Most patients can be differentiated in two groups, i.e. *nonerosive reflux disease (NERD)* and *erosive oesophagitis.* The first group are most common, patients have typical symptoms but they have no visible mucosal changes such as erosion or ulceration. The second group have endoscopically visible injuries such as mucosal inflammation, swelling or irritation and without recent acid suppressive therapy. But responsiveness to acid suppression therapy, abnormal reflux monitoring, or the identification of specific novel endoscopic findings support the diagnosis. First endoscopic abnormalities are areas of patchy erythema and red streaks.[5,6]

Histological features are diagnostically important. All changes tend to be patchy, so it is easy to miss diagnostic ones on a single biopsy. Changes are also progressive, or even regressive in case of proper therapy. The most common finding is basal cell hyperplasia without inflammation. The normal basal cell layer is less than 15 % of the squamous epithelial thickness, but in the case of acid reflux increases to more than

50 %, with elongated and numerous stromal papillae. Other findings are more characteristic for erosive oesophagitis. Balloon cells are very common, since they develop in any damaged mucosa. Capillary ectasies develop in most patients and are seen on the top of lengthened papillae. Lymphocytes can be found to ten per high-powered field with elongated nuclear contours, while neutrophils are seen occasionally in the area of an ulcer or erosion. Eosinophils are more common in children than in adults and occur very early. There is no sensitive marker for reflux disease.[7]

Eosinophilic oesophagitis is recently increasing or is better recognized. Usually children present with food refusal and failure to thrive, with refractory reflux symptoms unresponsive to acid blockade and/or prokinetic treatment. Endoscopy reveals strictures, corrugation, multiple oesophageal rings, webs, vertical furrows, mucosal granularity, mucosal fragility with speck and exudate, even polypoid lesions. Eosinophils are characteristic for eosinophilic oesophagitis, especially significant oesophageal eosinophilia (>15 intraepithelial eosinophils per hpf) and eosinophilic microabscesses (more than 4 in a cluster). They are usually situated in the superficial layers, but deeper eosinophilic infiltrates may manifest oesophageal part of more generalized eosinophilic disease.[7,8]

Stomach

The stomach works as a secretory, motor, digestive, hormonal and mucosal barrier. The most fascinating thing is the mucosal capacity for acid fluid. Histologically, stomach epithelium has three compartments: gastric pits and surface lining, mucous neck region and glands. Their thickness defines different gastric zones. The gastric pits appear macroscopically mostly the same even though their depth glands have changed in different stomach zone.

Endoscopy and biopsies are routinely used in initial diagnostic work-up and therapy evaluation for gastritis, peptic disease, *Helicobacter* infection and malignant proliferation. Histological examination may differentiate between specific forms of gastritis (eosinophilic, lymphocytic, granulomatous) and grade, extent and topography of lesions. Since gastric histology varies from area to area and many diseases are patchy, more biopsies always need to be taken from lesions as well as from other areas.

Gastric inflammatory diseases can be grouped into gastritis and gastropathy, according to the presence of inflammation. Gastritis is a consequence of infections, autoimmune or hypersensitive and drug reactions. It is important to determine the extent of inflammatory changes in the stomach but also trough the stomach wall. Other findings in biopsies may be present: surface epithelial damage, superficial stromal haemorrhage, metaplasia, endocrine cell hyperplasia, intraepithelial lymphocytosis, granulomas, apoptosis and microorganisms.[5]

In paediatric population, focal stomach lesions are extremely rare, most frequent findings are follicular or macronodular gastritis. Histologically, this is chronic, lymphocytic inflammation of mild to moderate grade, in antral and/or corporal area. Differential diagnosis includes *Helicobacter pylori* infection, bile reflux, autoimmune and allergic response, some drug use, but also less common Crohn's and coeliac disease.

Helicobacter pylori gastritis can exhibit indifferent histological features: as an infiltration of polymorphonuclear neutrophils, as a mixed infiltrate in the lamina propria and as a formation of lymphoid follicles. Microorganisms are found within the gastric mucous layer and frequently accumulate in groups at the apical side of gastric surface cells, occasionally in the lower portions of the gastric foveolae and rarely within the deeper areas of mucosa in association with glandular cells. As the infection lasts, *Helicobacter pylori* colonizes proximally and atrophy and metaplasia occur.[3]

In Crohn's disease, the stomach is involved in one third of the patients. Endoscopic findings include patchy or streaky mucosal reddening, edema, single or multiple nodularities, a cobblestone appearance, rigidity of the antrum wall, narrowing of the lumen, aphthoid erosions and linear or serpiginous

ulcers. Gastric epitheloid granuloma and giant cells could be found; they are characteristic but not diagnostic, and it is necessary to exclude other entities, such as sarcoidosis and histoplasmosis infection, and to check the gut as well. In immunosuppresed children, granulomatous gastritis is more frequent and is caused by tuberculosis or fungal infection. Endoscopic and/or histological gastric involvement in Crohn's disease may be present in the absence of upper gastrointestinal symptoms and may precede diagnostic findings in the small and large bowel.

In coeliac disease there is dense lymphocytic infiltration of the surface and foveolar epithelium, but also of the lamina propria. Duodenal mucosa and biopsies must be checked. Patients with corpus-predominant lymphocytic gastritis are unlikely to have duodenal pathology, whereas those with an antrum-predominant or a diffuse pattern have a 50 % chance of coexistent villous atrophy.[2,3]

Small bowel

Chronic diarrhoea and failure to thrive are main reasons for endoscopy and mucosal biopsy in children.

The first thought is coeliac disease. Endoscopic changes are scalloping, a mosaic pattern and flattening or paucity of the folds. These findings are not specific in childhood. Obtaining multiple biopsies is crucial for diagnosis. The typical flattening of villi can be patchy and easily missed. Histological examination shows the loss of normal villous structure with severe shortening up to complete absence (flat mucosa) of the villi. The intestinal crypts are markedly elongated and hyperplastic. Another typical finding is an increase in the number of intraepithelial lymphocytes.[9,10]

In differential diagnosis, some other entities such as malnutrition, common variable immunodeficiency, protein allergies, some infectious bacterial and parasitic gastroenteritis, stasis, autoimmune enteropathy, the Zollinger-Ellison syndrome and inflammatory bowel disease must be excluded, but crypts are less hyperplastic. Megaloblastic anaemia, radiation and chemotherapy should also be considered.[11]

Some diseases of villi are rare though characteristic, and histological examination provides a definitive diagnosis. They include diseases such as intestinal lymphangiectasia, microvillous inclusion disease, tufting enteropathy, abetalipoproteinemia, chylomicron retention disease, amyloidosis, Whipple disease, etc.[12]

Also important is to know the drugs that may cause malabsorption or intestinal transport inhibition, as methotrexate, azatioprine, erythromycin, cyclamates and antineoplastic agents.[13]

Large bowel

Normal endoscopic view of colonic mucosa is glistening salmon-pink with a visible network of branching vessels seen beneath the mucosa. The smoothness of the mucosal surface is the hallmark of a healthy colon and there is a lack of contact bleeding, friability or exudates. Histological, the mucosa appears flat with normal crypt density, undistorted crypt architecture, intact surface epithelium, normal mucin content and without any neutrophil infiltration.[14]

Crohn's disease starts with focal aphthous ulcers that gradually enlarge to linear and transverse ulcers. Intervening mucosa is normal. More severe disease causes nodularity with typical cobblestone appearance, but also strictures and stenosis. Terminal ileum is most common site of Crohn's disease. Normally, ileal mucosa is velvet-like, with smoother raised areas (Peyer's patches) and lymphonodular hyperplasia. Ileitis with granulomas may be only finding of Crohn's disease. Ileoscopy may help in diagnosis of other causes such infection with tuberculosis or Yersinia.[14]

Mucosa that appears grossly normal may reveal abnormalities on histological examination. Sometime is histological diagnosis a problem because only the mucosa and superficial submucosa are available for examination. In the early phases of Crohn's disease, changes may resemble to infectious colitis with infiltration of the crypts by polymorphonuclear leukocytes and distor-

tion of crypt architecture. Fibrosis and histiocytic proliferation can be found in the submucosa but most important sign is focal inflammation or transmural extension trough the bowel wall. Compact sarcoidlike granulomas are characteristic for Crohn's disease diagnosis. Must not be changed for mucin granulomas which include mature macrophages and foreign body-type giant cells which are present in any type of crypt destruction. They consist of small, localized aggregates of epitheloid histiocytes with or without Langerhans giant cells, surrounded with lymphocytes. Microgranulomas consist of only a few histiocytes and are easily overlooked. It number progressively increase in number from the ileum to the rectum and also occur in other tissues. Occasionally funding of microorganism is probably secondary infection.[15,16]

In ulcerative colitis earliest changes are diffuse erythema and dull appearance of the vascular architecture due to vascular congestion and edema. Contact bleeding and friability are often. Than ulcers appeared within a background of diffuse colonic inflammation. The colonic mucosa is continuously involved and finally forms pseudopolyps. The inflammatory infiltrate is typically confined to mucosa, but in severe disease may extend to the submucosa. Cell infiltrate consist of plasma cells, lymphocytes and neutrophils, but also of mast cells and eosinophils. Neutrophils are usually in crypts and cause cryptitis, crypt abscess and goblet cell mucin depletion.

In indeterminate colitis is important to exclude infections, drugs, malignancy, vasculitis and autoimmune diseases. A difference to the Crohn's disease is absence of lymphoid aggregates, granulomas and skips areas. A difference to the ulcerative colitis is rectal sparing, focal inflammation or deep fissuring ulceration. Upper endoscopy usually helps.[17,1]

Conclusion

For properly specimen interpretation, an effective dialogue between the pathologist and the clinician, is necessary. For diagnosis of gastrointestinal diseases in children and adolescent, it is important to connect clinical data with patohystologic findings because of proper therapy and better outcome.

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